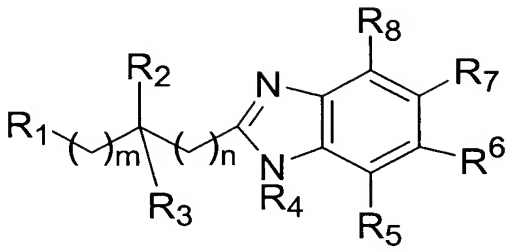
Claims

We Claim:

1. A compound of Formula (I):



(I)

wherein

m is an integer of from 0 to 3;

n is an integer of from 0 to 3;

R_1 comprises aryl;

R_2 comprises

a) a group of the formula $-N(R_9R_{10})$, $-NHC(O)R_9$, or $-NHC(O)OR_9$;

b) a group of the formula $-OR_9$;

c) a group of the formula $-SR_9$, $-SOR_9$, $-SO_2R_9$, $-SO_2NHR_9$, or $-SO_2N(R_9R_{10})$;

wherein R_9 and R_{10} independently comprise

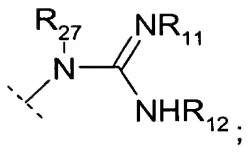
1) –H;

2) –Aryl;

3) a group comprising

a) $-C_{1-6}$ alkyl;

c) $-C_{1-6}$ alkylaryl;

d)  ;

e) –aryl;

f) -C_{1-6} alkyl; or

g) -C_{1-6} alkylaryl;

R_3 and R_4 independently comprise

a) H;

b) –aryl;

c) -C_{1-6} alkyl;

d) -C_{1-6} alkylaryl; or

e) -C_{1-6} alkoxyaryl;

R_5, R_6, R_7, and R_8 independently comprise

a) -H;

b) -C_{1-6} alkyl;

c) –aryl;

d) -C_{1-6} alkylaryl;

e) -C(O)-O-C_{1-6} alkyl;

f) -C(O)-O-C_{1-6} alkylaryl;

g) -C(O)-NH-C_{1-6} alkyl;

h) -C(O)-NH-C_{1-6} alkylaryl;

i) -SO_2-C_{1-6} alkyl;

j) -SO_2-C_{1-6} alkylaryl;

k) -SO_2-aryl;

l) -SO_2-NH-C_{1-6} alkyl;

m) -SO_2-NH-C_{1-6} alkylaryl;

n) -C(O)-C_{1-6} alkyl;

o) -C(O)-C_{1-6} alkylaryl;

p) -Y-C_{1-6} alkyl;

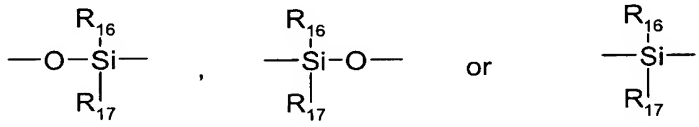
q) -Y-aryl;

r) -Y-C-$_{1-6}$ alkylaryl;

s) -Y-C_{1-6} alkylene-$NR_{13}R_{14}$; or

t) -Y-C_{1-6} alkylene-W-R_{15};

wherein Y and W independently comprise -CH_2-, -O-, -N(H), -S-, SO_2-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -$NHSO_2$-, -SO_2N(H)-, -C(O)-O-, -$NHSO_2$NH-, -O-CO-,



;

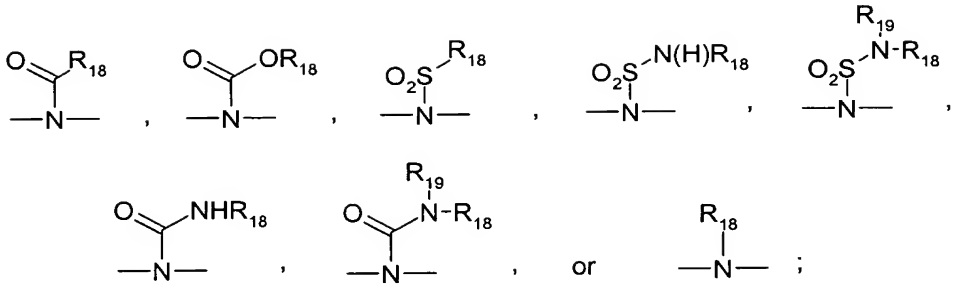
R_{16} and R_{17} independently comprise aryl, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, or C_1-C_6 alkoxyaryl;

R_{15} independently comprise aryl, C_1-C_6 alkyl, or C_1-C_6 alkylaryl; or

u) halogen, hydroxyl, cyano, carbamoyl, or carboxyl;

R_{11}, R_{12}, R_{13}, and R_{14} independently comprise hydrogen, aryl, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, or C_1-C_6 alkoxyaryl;

R_{13} and R_{14} may be taken together to form a ring having the formula -$(CH_2)_o$-X-$(CH_2)_p$- bonded to the nitrogen atom to which R_{13} and R_{14} are attached, and/or R_{11} and R_{12} may, independently, be taken together to form a ring having the formula -$(CH_2)_o$-X-$(CH_2)_p$- bonded to the atoms to which R_{11} and R_{12} are connected, wherein o and p are, independently, 1, 2, 3, or 4; X comprises a direct bond, –CH_2-, -O-, -S-, -$S(O_2)$-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -$NHSO_2$-, -SO_2N(H)-, -C(O)-O-, -O-C(O)-, -$NHSO_2$NH-,

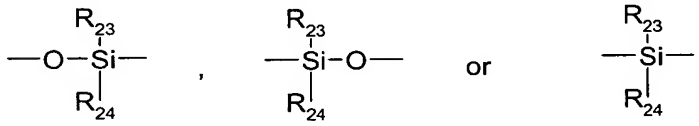


wherein the aryl and/or alkyl group(s) in R_1, R_2, R_3, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12}, R_{13}, R_{14} R_{15}, R_{16}, R_{17}, R_{18}, and R_{19} may be optionally substituted 1-4 times with a substituent group, wherein said substituent group(s) or the term substituted refers to groups comprising:

a) -H;

b) -Z-C_{1-6} alkyl;
-Z-aryl;
-Z-C-$_{1-6}$ alkylaryl;
-Z-C_{1-6}-alkyl-$NR_{20}R_{21}$; and
-Z-C_{1-6}-alkyl-W-R_{22};

wherein Z and W independently comprise -CH_2-, -O-, -N(H), -S-, SO_2-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -$NHSO_2$-, -SO_2N(H)-, -C(O)-O-, -$NHSO_2NH$-, -O-CO-,



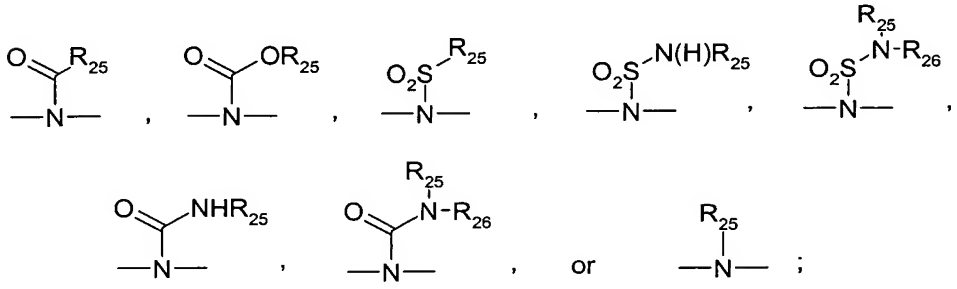
wherein;

R_{20} and R_{21} independently comprise hydrogen, aryl, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, or C_1-C_6 alkoxyaryl; and

R_{22}, R_{23}, and R_{24} independently comprise aryl, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, or C_1-C_6 alkoxyaryl; or

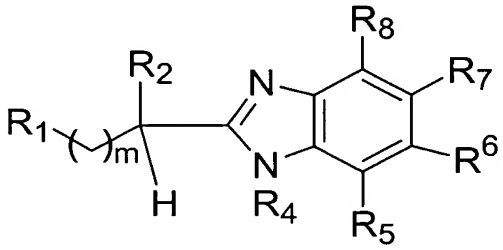
c) halogen, hydroxyl, cyano, carbamoyl, or carboxyl; and

R_{20} and R_{21} may be taken together to form a ring having the formula $-(CH_2)_q-X-(CH_2)_r-$ bonded to the nitrogen atom to which R_{20} and R_{21} are attached wherein q and r are, independently, 1, 2, 3, or 4; X comprises a direct bond, $-CH_2-$, -O-, -S-, $-S(O_2)-$, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, $-NHSO_2-$, $-SO_2N(H)-$, -C(O)-O-, -O-C(O)-, $-NHSO_2NH-$,



R_{25}, R_{26}, and R_{27} independently comprise hydrogen, aryl, C_1-C_6 alkyl, or C_1-C_6 alkylaryl; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

2. The compound of claim 1, wherein m is an integer of from 0 to 3; n is 0; R_3 is hydrogen as represented by the formula (II)



(II)

and wherein

R_1 comprises an aryl group;

R_2 comprises a group of the formula $-N(R_9R_{10})$, $-NHC(O)R_9$, or $-NHC(O)OR_9$;

wherein R_9 and R_{10} independently comprise

1) –H;

2) –Aryl; or

3) a group comprising -C_{1-6} alkyl or -C_{1-6} alkylaryl;

R_4 comprises

a) H;

b) –aryl;

c) -C_{1-6} alkyl;

d) -C_{1-6} alkylaryl; or

e) -C_{1-6} alkoxyaryl;

R_5, R_6, R_7, and R_8 independently comprise

a) -H;

b) -C_{1-6} alkyl;

c) –aryl;

d) -C_{1-6} alkylaryl;

e) -C(O)-O-C_{1-6} alkyl;

f) -C(O)-O-C_{1-6} alkylaryl;

g) -C(O)-NH-C_{1-6} alkyl;

h) -C(O)-NH-C_{1-6} alkylaryl;

i) -SO_2-C_{1-6} alkyl;

j) -SO_2-C_{1-6} alkylaryl;

k) -SO_2-aryl;

l) -SO_2-NH-C_{1-6} alkyl;

m) -SO_2-NH-C_{1-6} alkylaryl

n) -C(O)-C_{1-6} alkyl;

o) -C(O)-C_{1-6} alkylaryl;

p) -Y-C_{1-6} alkyl;

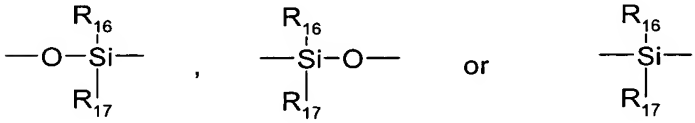
q) -Y-aryl;

r) -Y-C_{-1-6} alkylaryl;

s) -Y-C_{1-6} alkylene-$NR_{13}R_{14}$; or

t) -Y-C_{1-6} alkylene-W-R_{15};

wherein Y and W independently comprise -CH_2-, -O-, -N(H), -S-, SO_2-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -$NHSO_2$-, -$SO_2N(H)$-, -C(O)-O-, -$NHSO_2NH$-, -O-CO-,



;

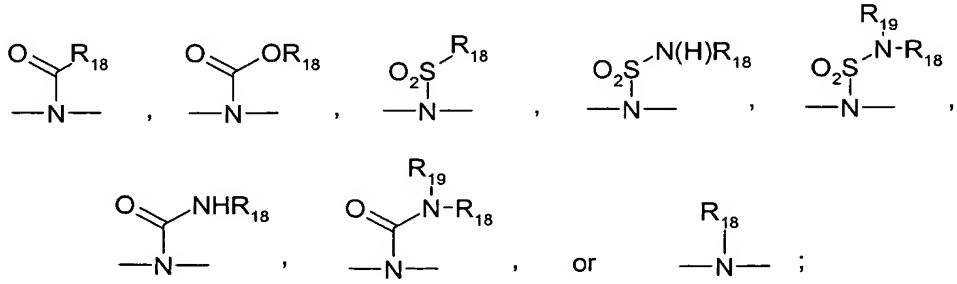
R_{16} and R_{17} independently comprise aryl, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, or C_1-C_6 alkoxyaryl;

R_{15} comprises aryl, C_1-C_6 alkyl, or C_1-C_6 alkylaryl, or

u) halogen, hydroxyl, cyano, carbamoyl, or carboxyl;

R_{13}, and R_{14} independently comprise hydrogen, aryl, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, or C_1-C_6 alkoxyaryl;

R_{13} and R_{14} may be taken together to form a ring having the formula -$(CH_2)_o$-X-$(CH_2)_p$- bonded to the nitrogen atom to which R_{13} and R_{14} are attached, wherein o and p are, independently, 1, 2, 3, or 4; X comprises a direct bond, –CH_2-, -O-, -S-, -S(O$_2$)-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -$NHSO_2$-, -$SO_2N(H)$-, -C(O)-O-, -O-C(O)-, -$NHSO_2NH$-,



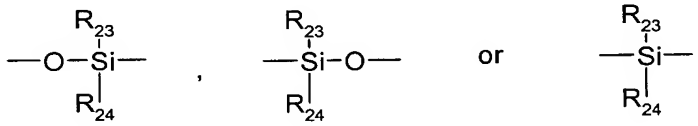
and wherein the aryl and/or alkyl group(s) in R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{13}, R_{14} R_{15}, R_{16}, R_{17}, R_{18}, and R_{19} may be optionally substituted 1-4 times with a substituent

group, wherein said substituent group(s) or the term substituted refers to groups comprising:

a) -H;

b) -Z-C_{1-6} alkyl;
-Z-aryl;
-Z-C_{-1-6} alkylaryl;
-Z-C_{1-6}-alkyl-$NR_{20}R_{21}$; and
-Z-C_{1-6}-alkyl-W-R_{22};

wherein Z and W independently comprise -CH_2-, -O-, -N(H), -S-, SO_2-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -$NHSO_2$-, -$SO_2N(H)$-, -C(O)-O-, -$NHSO_2NH$-, -O-CO-,



;

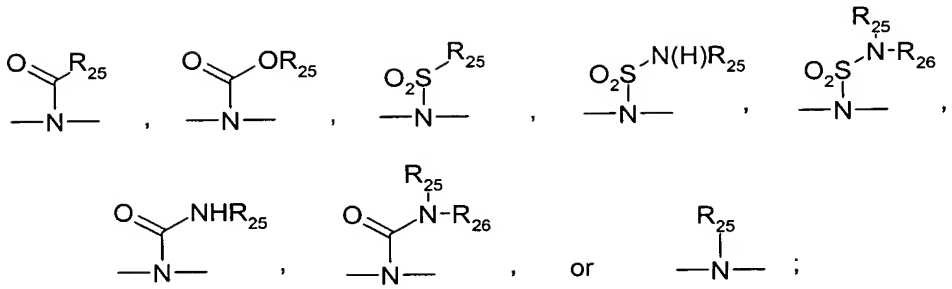
wherein;

R_{20} and R_{21} independently comprise hydrogen, aryl, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, or C_1-C_6 alkoxyaryl; and

R_{22}, R_{23}, and R_{24} independently comprise aryl, C_1-C_6 alkyl, C_1-C_6 alkylaryl, C_1-C_6 alkoxy, or C_1-C_6 alkoxyaryl; or

c) halogen, hydroxyl, cyano, carbamoyl, or carboxyl; and

R_{20} and R_{21} may be taken together to form a ring having the formula -$(CH_2)_q$-X-$(CH_2)_r$- bonded to the nitrogen atom to which R_{20} and R_{21} are attached wherein q and r are, independently, 1, 2, 3, or 4; X comprise a direct bond, –CH_2-, -O-, -S-, -$S(O_2)$-, -C(O)-, -CON(H)-, -NHC(O)-, -NHCON(H)-, -$NHSO_2$-, -$SO_2N(H)$-, -C(O)-O-, -O-C(O)-, -$NHSO_2NH$-,



R_{25}, R_{26}, and R_{27} independently comprise hydrogen, aryl, C_1-C_6 alkyl, or C_1-C_6 alkylaryl; or a pharmaceutically acceptable salt, solvate or prodrug thereof.

3. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-tert-butoxycarbonylamino-1-ethyl]-3-butyl-5-(3-diethylamino-1-propoxy)benzimidazole.

4. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-amino-1-ethyl]-3-butyl-5-(3-diethylamino-1-propoxy)benzimidazole Trihydrochloride.

5. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-tert-butoxycarbonylamino-1-ethyl]-3-butyl-6-(3-diethylamino-1-propoxy)benzimidazole.

6. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-amino-1-ethyl]-3-butyl-6-(3-diethylamino-1-propoxy)benzimidazole.

7. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-tert-butoxycarbonylamino-1-ethyl]-6-(3-diethylamino-1-propoxy)benzimidazole.

8. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-amino-1-ethyl]-6-(3-diethylamino-1-propoxy)benzimidazole.

9. The compound of claim 1, wherein the compound comprises 2-[2-(3-Benzyloxyphenyl)-1-(tert-butoxycarbonylamino)-1-ethyl]-3-butyl-5-(3-diethylamino-1-propoxy)benzimidazole.

10. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Ethoxyphenyl)-1-(tert-butoxycarbonylamino)-1-ethyl]-3-butyl-5-(3-diethylamino-1-propoxy)benzimidazole.

11. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-(4-Chloro)phenethoxy)phenyl)-1-(tert-butoxycarbonylamino)-1-ethyl]-3-butyl-5-(3-diethylamino-1-propoxy)benzimidazole.

12. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-(tert-butoxycarbonylamino)-1-ethyl]-3-(3-diethylamino-1-propyl)-5-(3-diethylamino-1-propoxy)benzimidazole.

13. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-(tert-butoxycarbonylamino)-1-ethyl]-3-ethyl-5-(3-diethylamino-1-propoxy)benzimidazole.

14. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-amino-1-ethyl]-3-(3-diethylamino-1-propyl)-5-(3-diethylamino-1-propoxy)benzimidazole.

15. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-(tert-butoxycarbonylamino)-1-ethyl]-3-benzyl-5-(3-diethylamino-1-propoxy)benzimidazole.

16. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-amino-1-ethyl]-3-benzyl-5-(3-diethylamino-1-propoxy)benzimidazole.

17. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-(tert-butoxycarbonylamino)-1-ethyl]-3-propyl-5-(3-diethylamino-1-propoxy)benzimidazole

18. The compound of claim 1, wherein the compound comprises 2-[(1R)-2-(4-Benzyloxyphenyl)-1-amino-1-ethyl]-3-propyl-5-(3-diethylamino-1-propoxy)benzimidazole.

19. A pharmaceutical composition comprising the compound of Formula (I) as claimed in claim 1, and one or more pharmaceutically acceptable carriers, excipients, or diluents.

20. The pharmaceutical composition of to claim 19, in the form of an oral dosage or parenteral dosage unit.

21. The pharmaceutical composition of claim 19, wherein said compound is administered as a dose in a range from about 0.01 to 500 mg/kg of body weight per day.

22. The pharmaceutical composition of claim 19, wherein said compound is administered as a dose in a range from about 0.1 to 200 mg/kg of body weight per day.

23. The pharmaceutical composition of claim 19, wherein said compound is administered as a dose in a range from about 0.1 to 100 mg/kg of body weight per day.

24. The pharmaceutical composition of claim 19, further comprising one or more therapeutic agents selected from the group consisting of alkylating agents, antimetabolites, plant alkaloids, antibiotics, hormones, biologic response modifiers, analgesics, NSAIDs, DMARDs, glucocorticoids, sulfonylureas, biguanides, insulin, cholinesterase inhibitors, antipsychotics, antidepressants, and anticonvulsants.

25. A method for the inhibition of the interaction of RAGE with its physiological ligands, which comprises administering to a subject in need thereof, at least one compound of Formula (I) as claimed in claim 1.

26. The method of claim 25, wherein the ligand(s) is(are) selected from advanced glycated end products (AGEs), S100/calgranulin/EN-RAGE, β-amyloid and amphoterin.

27. A method for treating a disease state selected from the group consisting of acute and chronic inflammation, symptoms of diabetes, vascular permeability, nephropathy, atherosclerosis, retinopathy, Alzheimer's disease, erectile dysfunction, and tumor invasion and/or metastasis, which comprises administering to a subject in need thereof a therapeutically effective amount of at least one compound of Formula (I) as claimed in claim 1.

28. A method of prevention and/or treatment of RAGE mediated human diseases comprising administration to a human in need thereof a therapeutically effective amount of a compound of Formula (I) as claimed in claim 1, wherein a therapeutically effective amount comprises sufficient compound to at least partially inhibit the binding of a ligand to the RAGE receptor.

29. The method of claim 28, further comprising administering to a subject in need thereof at least one adjuvant and/or additional therapeutic agent(s).

30. The method of claim 29, wherein said therapeutic agents are selected from the group consisting of alkylating agents, antimetabolites, plant alkaloids, antibiotics, hormones, biologic response modifiers, analgesics, NSAIDs, DMARDs, glucocorticoids, sulfonylureas, biguanides, insulin, cholinesterase inhibitors, antipsychotics, antidepressants, and anticonvulsants.

31. The method of claim 28, wherein the RAGE mediated human disease comprises acute and/or chronic inflammation.

32. The method of claim 28, wherein the RAGE mediated human disease comprises abnormal vascular permeability.

33. The method of claim 28, wherein the RAGE mediated human disease comprises nephropathy.

34. The method of claim 28, wherein the RAGE mediated human disease comprises atherosclerosis.

35. The method of claim 28, wherein the RAGE mediated human disease comprises retinopathy.

36. The method of claim 28, wherein the RAGE mediated human disease comprises Alzheimer's disease.

37. The method of claim 28, wherein the RAGE mediated human disease comprises erectile dysfunction.

38. The method of claim 28, wherein the RAGE mediated human disease comprises tumor invasion and/or metastasis.